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EDITORIAL COMMENT

Torrent or Torment From the Tubules?*

Challenge of the Cardiorenal Connections

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The increasing use of angiotensin-converting enzyme inhibitors and beta-blockers has delayed the progression of and decreased mortality in heart failure. As more patients survive into advanced stages of disease, however, it is increasingly difficult to maintain optimal fluid balance while preserving renal function. The complexity of cardiorenal connections was the subject of recent review by a working group of the National Heart, Lung, and Blood Institute (1). The current study by Paterna et al. (2) in this issue of the *Journal* suggests surprising efficacy of a strategy to enhance both acute and chronic diuretic response by enhanced sodium intake. This counterintuitive approach underlines the need for better understanding of factors that regulate sodium and water handling in chronic heart failure.

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CHANGING VIEW OF CARDIORENAL CONNECTIONS DURING DISEASE PROGRESSION

The cardiorenal syndrome can be defined narrowly as worsening renal function limiting diuresis despite obvious clinical volume overload (3). An elevation in creatinine of 0.3 mg/dl or proportional rises of 25% during diuresis are observed in more than 20% of heart failure hospitalizations (4). Originally described in patients with low ejection fraction, this syndrome is now recognized to occur as often in patients admitted with heart failure and preserved ejection fraction, many of whom have hypertension (5), diabetes, and impaired baseline renal function. Risk increases with longer history of heart failure and high chronic diuretic doses. Worsening indices of renal function limit symptomatic and neurohormonal therapy, lead to longer hospital stay, and predict higher rate of early rehospitalization and death.

A classic conception of the cardiorenal interaction in heart failure progression begins with a postulated early reduction in cardiac output that stimulates systemic and intrarenal responses to retain fluid and restores cardiac output at new circulating volume. This reduction is followed by a postulated subsequent progression of cardiac dysfunction that further diminishes cardiac output, impairing renal blood flow, and further activating responses that decrease renal function but fail to normalize cardiac output. At the late stage of heart failure, the cardiorenal syndrome has been attributed to a postulated further decrease in cardiac output during aggressive diuresis to relieve symptoms.

Although internally consistent, this conception is dissolving. In asymptomatic patients with left ventricular dysfunction, an inability to excrete a volume load precedes any evidence of diminution in cardiac output (6). It was once thought that very high filling pressures were necessary to maintain stroke volume from the dilated ventricle, thus providing one explanation for the chronic stimulus for fluid retention. However, it is now well established that stroke volume is maximal at near-normal levels of filling pressure for most patients with chronic dilated heart failure (7). Higher filling pressures cause increasing wall stress, mitral regurgitation, and eventually pulmonary hypertension and secondary right ventricular dysfunction. Right-sided congestion then compromises food intake and hepatic function, leading to malnutrition. The fluid retention far exceeds that needed for optimal circulatory function. Once thought to be only the manifestation of worsening heart failure, fluid retention may in fact be a major factor responsible for disease progression from asymptomatic through late-stage disease (8).

The cardiorenal syndrome at the late stage of disease is evident in the patient with multiple hospitalizations for congestion, with diuresis interrupted each time by increasing levels of creatinine. This diminution in renal function often is dismissed as "pre-renal," with implications that have not advanced understanding or therapy. When actually measured, central cardiac output and estimated renal perfusion pressure usually have not been reduced during diuresis (3,9) but often have improved as the result of forward redistribution of mitral regurgitant flow. It remains possible that complex changes in regional flow distribution may occur without changes in vasodilator dosing or calculated total vascular resistance.

A fundamental aspect from asymptomatic through late-stage heart failure may be the establishment of an elevated volume set point that exceeds that for optimal circulatory function (9). Factors involved in this set point include cardiac output and activation of renin-angiotensin-aldosterone and sympathetic systems. A role also is assigned to natriuretic peptides, but the relationship of circulating levels to the most active peptides and their coupling to biologic responses is still obscure. Under complex control, vasopressin remains a strong contender as a player in diuretic resistance in advanced disease, but with high

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inter-individual variation. There is also a potential contribution of blunted neural input from atrophied stretch receptors in chronically distended atriopulmonary beds, which has been well-demonstrated in dog models of chronic volume overload (10).

In addition to all of the other factors involved, it is likely that the cardiorenal interactions will demonstrate strong influence from genetic polymorphisms that affect neurohormonal responses and sodium avidity, as has been observed for hypertension (9). Pre-existing renal impairment accelerates disease progression at all stages. Untangling the cardiorenal syndrome in humans is further complicated because progression has occurred in the milieu of chronic neurohormonal antagonists and diuretic therapy, which stimulate chronic compensatory responses (11).

GIVE SODIUM A CHANCE?

In the contemporary setting, where the cardiorenal syndrome occurs in more than 250,000 hospitalizations annually (12), the current study challenges accepted concepts about acute and chronic diuresis (1). Results from this small but elegant randomized study of 94 patients hospitalized with clinical volume overload suggest that the administration of sodium may paradoxically treat the sodium-retaining state. For acute diuresis, very high doses of furosemide (500 to 1,000 mg) were administered twice daily with either hypertonic saline or vehicle infusion concomitantly. Patients receiving hypertonic saline had greater volume loss and were discharged sooner, with better renal function and higher serum sodium.

During the chronic phase, the higher salt group had a target daily sodium intake of 2.8 g compared with 1.8 g in the control group. Both groups were restricted to 1 liter of fluid intake daily, unlike many patients for whom fluid is limited to 2 liters daily or not restricted. In the current study, patients were reassessed at one month, at which time serum B-type natriuretic peptide levels remained lower in the group with higher sodium intake. Bioimpedance measurements have not been consistently validated for volume state in heart failure but were consistent with lower total body volume in the higher sodium group. There were 12 readmissions in 46 patients during one month in the usual therapy group compared with none for the higher sodium group. Longer follow-up with this therapy is available from a previous single-blind study of 107 patients by the same authors (13), in which 43 of 54 patients on usual therapy were readmitted compared with 25 of 53 patients during a 31-month mean follow-up, and mortality was reduced in the treated group. The event rates differ markedly between these two studies but together suggest that relaxing sodium restriction to 2.8 g daily while maintaining severe fluid restriction to 1 liter daily may improve clinical outcomes.

Attempting to place these results into the context of what is known about cardiorenal connections emphasizes how little is understood in the human model of fluid retention during chronic therapy for heart failure. Reviewing the previous work, Drazner and Palmer (14) provided lucid speculation about the effects of this novel therapy. For the acute phase, why does excess saline load facilitate overall diuresis? The difference between the amounts of sodium excreted acutely by the two groups is largely accounted for by the higher sodium intake of the high sodium group; therefore, the difference is not in efficacy of sodium excretion. Rather, there was a larger amount of free water loss in this group. This may relate in part to an acute osmotic effect of hypertonic saline to increase mobilization of extravascular fluid into the central circulation and renal circulation. Direct intratubular effects of sodium flooding may overwhelm the postdiuretic NaCl retention and over time may reduce the diuretic "braking" phenomenon by which fluid escaping past the ascending limb is captured downstream (11).

Although neurohormone levels were not assayed, they may have been suppressed by hypertonic saline. Both increased intravascular volume and greater delivery of sodium to the distal tubule should inhibit the renin-angiotensin-aldosterone system. Inhibition of aldosterone release could explain the lower relative potassium excretion in the high sodium group. Reduction in angiotensin II levels could lead also to a decrease in vasopressin release despite temporary increase in serum osmolarity. There may also be a small contribution of increased intravascular volume to stimulation of the low-pressure and high-pressure baroreceptors that inhibit vasopressin release. Decreased levels of vasopressin could reduce the aquaporin channels through which water is reabsorbed, leading to the greater free water excretion observed. Reduced vasopressin also might also decrease compensatory over-expression of the sodium transporter in the ascending limb, which diminishes diuretic effect (15). The marked increase in low serum sodium levels is consistent with vasopressin inhibition.

The 2.8 g/day of the higher sodium group is less than most average diets and therefore would still be considered sodium restriction (although higher than the 2-g daily recommended to many patients). Mild sodium restriction clearly appears beneficial to lower blood pressure in hypertension and has been assumed beneficial to delay the need for diuretic therapy in early heart failure. High sodium intake has been observed to lessen efficacy of diuretic therapy once instituted, presumably because of enhanced distal tubular reabsorption. Should sodium restriction be mild or severe, and how should it differ for individual patients as disease progresses? It is often assumed that a given intervention or restriction should be intensified if the condition progresses, but this has rarely been proven. In hypertension, a low-sodium diet potentiates the activation of the sympathetic and renin-angiotensin system and likely does the same in heart failure. Perfusion in the upright posture may be particularly compromised by low sodium intake, with associated neurohormonal response. The key distinction here may be between mild and severe sodium restriction.

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Does sodium intake affect serum sodium levels in heart failure? Hyponatremia has long been associated with worse outcome (16), assumed to reflect severe circulatory compromise amenable only to restriction of free water or improvement of the circulatory state. The brief administration of hypertonic saline in this study was not sufficient to directly cause a sustained increase in serum sodium levels and therefore other mechanisms affecting osmolar regulation, such as those discussed previously, must be implicated. Is the increase in chronic sodium intake sufficient to directly account for the trend toward normalization of serum sodium levels, or does it again imply improved neurohormonal regulation? Additionally, the liberalization of chronic sodium restriction could promote better nutrition due to wider variety of voluntary nutrient intake.

Hyponatremia has multiple adverse consequences in terms of cardiac and peripheral muscle function, cardiac rhythm and, again, in relation to systemic circulatory integration. Resolution of hyponatremia is associated with better outcomes in heart failure. Serum sodium increased during hospitalization but information is not provided regarding hyponatremia after discharge in either study. As with other biomarkers, a therapy that increases serum sodium level cannot necessarily be presumed as favorable as spontaneous improvement. The legitimacy of a biomarker change during therapy requires validation for that specific intervention. In the first month of follow-up, the rate of hospitalization was lower in patients with less sodium restriction. It remains to be seen in which patients serum sodium concentration can be sustained by increased sodium intake and whether this creates or merely identifies patients more likely to do well.

PATIENT POPULATIONS

The patients studied had an average age of 74 years, ejection fraction 30%, and systolic blood pressure 146 mm Hg, similar to the previous trial (13,17). This population differs markedly from heart failure trial populations but is typical of patients hospitalized with heart failure in the community (17). The study excluded patients with levels of serum creatinine >2 mg/dl or blood urea nitrogen >60 mg/dl, those most likely to have diuretic resistance and worsening renal function. The boluses of loop diuretics used, 500 to 1,000 mg twice daily, are more than twice as high as customarily used during hospitalization, although total daily doses would be comparable to high-dose continuous infusions. Dosing of chronic diuretics for outpatients is not described. It is possible that the intensity of diuretic therapy created an opportunity for protective benefit from higher sodium intake that would not be realized with lower diuretic doses. Lastly, the volume restriction of 1 liter per day is rarely achieved or even suggested for most patients with chronic heart failure in the U.S. (18). The liquid taken with medications would consume much of that meager allotment. It is sometimes said that either sodium or fluid should be restricted but rarely both. With more liberal fluid consumption, would increased sodium intake have increased fluid retention and hospitalizations?

ACCEPTING THE CHALLENGE

Despite the restricted relevance of the protocol, this study raises important questions. There are insufficient data yet to routinely administer hypertonic saline to heart failure populations or liberalize oral sodium intake. However, new approaches should be enthusiastically considered for patients with progressive diuretic resistance, recurrent hospitalization, or worsening renal function that limits symptom relief in whom current therapy is failing. New agents under development include receptor antagonists for vasopressin and adenosine (19,20). If successful, these agents would be stacked on top of current regimens for maintaining fluid balance. This study indicates the need to challenge our current practice of chronic sodium restriction. We should also challenge how we dose diuretics, both acutely and chronically (11). Should aldosterone antagonists be titrated up in some patients to achieve primary diuresis? Should thiazides be used intermittently even before high-dose loop diuretics are required? When should diuretic resistance or renal dysfunction trigger the decrease or discontinuation of angiotensin-converting enzyme inhibitors? Will nesiritide improve diuresis and renal function in some of these patients (20)? Are there inotropic or other therapies with adverse effects that might nonetheless have overall benefit for some patients if they allow reduction in diuretic therapy? Key to a better understanding of these questions is the establishment of more routine quantitation of circulating volume, sodium, and water excretion and neurohormonal responses acutely and chronically during intervention.

The cardiorenal syndromes are consuming an increasing proportion of attention and resources for the management of heart failure. As the lightening threat of sudden death lessens, the clouds darken with the limitations of current therapy to maintain freedom from congestion while preserving renal function. Sodium administration alone is not likely to prevent or solve this problem, but the intriguing observations from this study provide direction for physiologic investigation and hopefully new strategies.

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